# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



| Applicant's or agent's file reference<br>81331-197 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/CA2004/001883 | International filing date *(day/month/year)*<br>27 October 2004 (27-10-2004) | Priority date *(day/month/year)*<br>27 October 2003 (27-10-2003) |

International Patent Classification (IPC) or national classification and IPC
IPC: A61K 38/28 ***(2006.01)*** , A61P 3/10 ***(2006.01)*** , A61K 38/16 ***(2006.01)*** , A61K 31/64 ***(2006.01)*** , A61K 31/4439 ***(2006.01)*** , A61K 31/198 ***(2006.01)***

Applicant
INNODIA INC. ET AL

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 14 sheets, as follows:
      [ ] sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. 1 and the Supplemental Box.
   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - [X] Box No. I Basis of the report
   - [X] Box No. II Priority
   - [X] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [ ] Box No. VII Certain defects in the international application
   - [X] Box No. VIII Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 15 August 2005 (15-08-2005) | 27 February 2006 (27-02-2006) |
| Name and mailing address of the IPEA/CA<br>Canadian Intellectual Property Office<br>Place du Portage I, C114 - 1st Floor, Box PCT<br>50 Victoria Street<br>Gatineau, Quebec K1A 0C9<br>Facsimile No.: 001(819)953-2476 | Authorized officer<br>Nicole Harris (819) 997-4541 |

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/CA2004/001883

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (Rules 12.3(a) and 23.1(b))

[ ] publication of the international application (Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

[ ] the international application as originally filed/furnished

[X] the description:

| | | | | |
|---|---|---|---|---|
| [X] | pages | 1, 4-15, and 17-19 | | as originally filed/furnished |
| [X] | pages* | 2, 2a, 2b, 3 and 16 | received by this Authority on | 15 August 2005 (15-08-2005) |
| [ ] | pages* | | received by this Authority on | |

[X] the claims:

| | | | | |
|---|---|---|---|---|
| [ ] | pages | | | as originally filed/furnished |
| [ ] | pages* | | as amended (together with any statement) under Article 19 | |
| [X] | pages* | 20-24 | received by this Authority on | 15 August 2005 (15-08-2005) |
| [ ] | pages* | | received by this Authority on | |

[X] the drawings:

| | | | | |
|---|---|---|---|---|
| [ ] | pages | | | as originally filed/furnished |
| [X] | pages* | 1-4 | received by this Authority on | 15 August 2005 (15-08-2005) |
| [ ] | pages* | | received by this Authority on | |

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [X] The amendments have resulted in the cancellation of:

[X] the description, pages 2, 3 and 16 as originally filed

[X] the claims, Nos. 1-28 as originally filed

[X] the drawings, sheets/figs pages 1-4 as originally filed

[ ] the sequence listing *(specify):*

[ ] any table(s) related to sequence listing *(specify):*

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify):*

[ ] any table(s) related to sequence listing *(specify):*

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

**Box No. II Priority**

1. [ ] This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   [ ] copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   [ ] translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. [ ] This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Remarks: The validity of the priority claims has not been considered because the International Searching Authority does not have in its possession a copy of the earlier applications whose priority has been claimed or, where required, a translation of those earlier applications. This opinion has nevertheless been established on the assumption that the relevant date (Rule 64.1) is the claimed priority date.

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

[ ] the entire international application

[X] claims Nos. 30-43

because:

[X] the said international application, or the said claims Nos. 30-43
relate to the following subject matter which does not require an international preliminary examination *(specify):*

Although claims 30-43 encompass methods of medical treatment of a human or animal which this Authority is not required to examine under Rule 67.1 (iv) of the PCT, the written opinion has been established on the basis of the alleged effects of the compounds referred to therein.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify):*

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed *(specify):*

[ ] no international search report has been established for said claims Nos.

[ ] a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

[ ] furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

[ ] a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-43 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | | YES |
| | Claims | 1-43 | NO |
| Industrial applicability (IA) | Claims | 1-43 | YES |
| | Claims | | NO |

2. Citations and explanations (Rule 70.7)

D1: EP 1206257, (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE), 22 May 2002

**Novelty and Inventive Step**

The problem to be solved by the present invention is to provide synergistic combinations of 4-hydroxyisoleucine (4-OH-Ile) and antidiabetic agents for treating diabetes.

D1 discloses insulinotropic activity of insulin, 4-hydroxyisoleucine (4-OH-Ile) and the combination of 4-OH-Ile and insulin in type II diabetic rats. The effect of the combination of 4-OH-Ile and insulin was greater than the effect of insulin or 4-OH-Ile when used alone. Pharmaceutical combinations of insulin and 4-OH-Ile are also disclosed. D1 is considered the closest prior art. D1 does not teach or suggest combinations of 4-hydroxyisoleucine (4-OH-Ile) and other antidiabetic agents or uses thereof in treating diabetes. Therefore, claims 1-43 appear to meet the requirements of Article 33(2) of the PCT with respect to novelty.

Predicting which combinations of drugs known to be useful in the treatment of diabetes would provide additive effects compared to the use of each drug individually would not be obvious to someone skilled in the art. However, claims 1-43 are merely directed towards pharmaceutical kits (claim 14-27), compositions (claim 28) and uses of said compositions in treating diabetes (claims 1-13, and 29-43) which encompass both synergistic and nonsynergistic 4-OH-Ile and antidiabetic agent combinations. Thus, given the state of the art, with regards to antidiabetic agents, it would be obvious to someone skilled in the art to combine 4-OH-Ile with other antidiabetic agents for the treatment of diabetes. Further, while synergistic combinations of 4-OH-Ile and other antidiabetic agents can not be predicted, combinations of 4-OH-Ile and insulin and one or more additional antidiabetic agents (claims 3, 16 and 32) would be presumed to retain the synergistic effects of the 4-OH-Ile and insulin combination, as disclosed in D1, and would be considered synergistic combinations used to treat diabetes. Additionally, since the combination of 4-OH-Ile and the antidiabetic agent, insulin, provided an additive effect, it would be reasonable for someone skilled in the art, without evidence to the contrary, to assume that other antidiabetic agents in combination with 4-OH-Ile would also provide additive effects compared to the use of the agents individually. As such, the pharmaceutical kits (claim 14-27), compositions (claim 28) and uses of said compositions in treating diabetes (claims 1-13, and 29-43) do not involve an inventive step (Article 33(3) of the PCT).

**Industrial Applicability**

For the assessment of claims 30-43 on the question of whether or not they define subject matter that has industrial applicability, no unified criteria exists in the PCT. Accordingly, although the methods *per se* defined in claims 30-43 relate to subject matter which this Authority is not obliged to examine under Rule 67.1 (iv) of the PCT, an opinion on the industrial applicability of claims 30-43 has been established based on the use of the 4-hydroxyisoleucine compositions referred to therein.

Claims 1-43 appear to meet the requirements of Article 33(4) of the PCT with respect to industrial applicability.

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1, 14, 28 and 30 do not comply with Article 6 of the PCT. The phrase "the following types of antidiabetic agents" lacks clarity. It is unclear whether said phrase is limited to the antidiabetic agents listed or also includes other antidiabetic agents of the "type" that is listed but not included in said claims.

Claims 1 and 28 do not comply with Article 6 of the PCT. Claims 1 and 28 are directed towards "4-hydroxyisoleucine and one or more antidiabetic agents". However, the number of antidiabetic agents in combination with 4-hydroxyisoleucine is ambiguous since it is unclear whether the term "the additional antidiabetic agents" (claim 1) and "said additional antidiabetic agents" (claim 28) refers to the "one or more antidiabetic agents" or to "antidiabetic agents" in addition to the "one or more antidiabetic agents" of the combinations.

Claims 17, 19-22, 24, 26 and 43 do not comply with Article 6 of the PCT. The terms "the additional antidiabetic agents" (claims 17, 19-22 , 24 and 26) and "the hydroxylated amino acid" (claims 26 and 43) lack antecedents.

Claim 29 does not comply with Article 6 of the PCT. The phrasing "use of a pharmaceutical kit", "for treating diabetes" is imprecise since it is the contents of the kit which is used for treating diabetes and not the kit *per se*.

Claim 30 does not comply with Article 6 of the PCT. The inclusion of "additional" in the phrase "one or more additional antidiabetic agents" causes confusion. Claim 30 is directed towards a method of using 4-hydroxyisoleucine and antidiabetic agents to treat diabetes. However, it is unclear whether "additional" pertains to the 4-hydroxyisoleucine or the antidiabetic agent of the combined treatment.

development of effective approaches to treatment is a primary concern in the field of medicine.

## Summary of the Invention

The invention provides methods of treating diabetes (type 1 diabetes or type 2 diabetes) in patients, which involve administering to the patients a hydroxylated amino acid (for example, 4-hydroxyisoleucine, e.g., the 2S,3R,4S isomer of 4-hydroxyisoleucine) and one or more additional antidiabetic agents, to obtain an improved (e.g., synergistic or additive) effect. Examples of additional antidiabetic agents that can be used in the invention include biguanides (e.g., metformin), sulfonylurea drugs, glinides, glitazones (e.g., thiazolidinediones, such as rosiglitazone maleate), glucagon-like peptide 1 receptor agonists (e.g., Exenatide®), and insulin. Other examples of antidiabetic (and other) agents that can be used in combination with hydroxylated amino acids according to the invention are listed below. In one example, 4-hydroxyisoleucine is combined with insulin and/or metformin, while in another example, 4-hydroxyisoleucine is combined with metformin and/or a thiazolidinedione. The hydroxylated amino acid and other antidiabetic agents can be administered at or about the same time as one another or at different times. Also included in the invention are pharmaceutical kits and compositions (e.g., tablets or capsules) that include combinations of the agents noted above and elsewhere herein.

The invention provides a method of treating diabetes in a patient, the method comprising administering to the patient 4-hydroxyisoleucine and one or more additional antidiabetic agents selected from the following types of antidiabetic agents: biguanides, sulfonylurea drugs, glinides, insulin-sensitizing agents, glucagon-like peptide 1 receptor agonists, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, imidazolines, glycogen phosphorylase inhibitors, oxadiazolidinediones, dipeptidyl peptidase-IV inhibitors, protein tyrosine phosphatase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 inhibitors, antihyperlipidemic agents, antilipidemic agents, peroxisome proliferator-activated receptor agonists, retinoid X receptor agonists, and antihypertensive agents.

The invention provides use of 4-hydroxyisoleucine and one or more antidiabetic agents in the manufacture of a medicament for treating diabetes, wherein the additional antidiabetic agent(s) is selected from the following types of antidiabetic agents:

biguanides, sulfonylurea drugs, glinides, insulin-sensitizing agents, glucagon-like peptide 1 receptor agonists, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, imidazolines, glycogen phosphorylase inhibitors, oxadiazolidinediones, dipeptidyl peptidase-IV inhibitors, protein tyrosine phosphatase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 inhibitors, antihyperlipidemic agents, antilipidemic agents, peroxisome proliferator-activated receptor agonists, retinoid X receptor agonists, and antihypertensive agents.

The invention provides a pharmaceutical kit comprising 4-hydroxyisoleucine and one or more antidiabetic agents selected from the following types of antidiabetic agents: biguanides, sulfonylurea drugs, glinides, insulin-sensitizing agents, glucagon-like peptide 1 receptor agonists, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, imidazolines, glycogen phosphorylase inhibitors, oxadiazolidinediones, dipeptidyl peptidase-IV inhibitors, protein tyrosine phosphatase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 inhibitors, antihyperlipidemic agents, antilipidemic agents, peroxisome proliferator-activated receptor agonists, retinoid X receptor agonists, and antihypertensive agents.

The invention provides a pharmaceutical composition comprising 4-hydroxyisoleucine, one or more antidiabetic agents and a pharmaceutically acceptable excipient, wherein said additional antidiabetic agent(s) is selected from the following types of antidiabetic agents: biguanides, sulfonylurea drugs, glinides, insulin-sensitizing agents, glucagon-like peptide 1 receptor agonists, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, imidazolines, glycogen phosphorylase inhibitors, oxadiazolidinediones, dipeptidyl peptidase-IV inhibitors, protein tyrosine phosphatase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 inhibitors, antihyperlipidemic agents, antilipidemic agents, peroxisome proliferator-activated receptor agonists, retinoid X receptor agonists, and antihypertensive agents.

The invention provides the use of a pharmaceutical kit of this invention or of a pharmaceutical composition of this invention, for treating diabetes in a patient.

The invention provides several advantages. For example, because the drug combinations described herein are used to obtain improved (e.g., synergistic or additive)

effects, it is possible to consider administering less of each drug, leading to a decrease in the overall exposure of patients to drugs, as well as any untoward side effects of any of the drugs. In addition, greater control of the disease may be achieved, because the drugs can combat the disease through different mechanisms.

Other features and advantages of the invention will be apparent from the following detailed description and the claims.

## Brief Description of the Drawings

Figure 1 is a bar graph showing additive stimulation of glucose uptake in 3T3-L1 differentiated adipocytes by the combination of insulin and ID 1101. Cells were exposed to the treatments for 0.5h, 1h, 2h, 4h or 5h. Treatments were: (1) Control; (2) 0.5 mM ID 1101; (3) 1 mM ID 1101; (4) Insulin $10^{-7}$ M; (5) 0.5 mM ID 1101 + Insulin $10^{-7}$ M; (6) 1 mM ID 1101 + Insulin $10^{-7}$ M.

Figures 2A, 2B, 2C and 2D are bar graphs showing changes in plasma glucose levels from baseline during an oral glucose tolerance test. AUC Delta OGTT is shown at Day 0 (Fig.2A), at Day 7 (Fig.2B); at Day 14 (Fig.2C) and at Day 21 (Fig. 2D). Treatments were: (1) Control NDC; (2) ID 1101 50 mg/kg BID; (3) ID 1101 100 mg/kg BID; (4) Rosiglitazone 1.5 mg/kg BID; (5) Rosiglitazone 5 mg/kg BID; (6) ID 1101 50 mg/kg + Rosiglitazone 1.5 mg/kg BID; (7) Control DIO.

Figure 3 is a bar graph showing the effect on insulin secretion in INS-1 beta cells of ID 1101 in combination with Glibenclamide. Treatments were: (1) 4.5 mM Glucose; (2) 0.1 mM ID 1101; (3) Glibenclamide $10^{-11}$ M; (4) 0.1 mM ID 1101 + Glibenclamide $10^{-11}$ M; (5) Glibenclamide $10^{-10}$ M; (4) 0.1 mM ID 1101 + Glibenclamide $10^{-10}$ M.

Figure 4 is a bar graph showing the effect on insulin secretion in INS-1 beta cells of ID 1101 in combination with $10^{-10}$ M or $10^{-9}$ M Exendin-4. White bars: Control buffer; Dashed bars: 0.01 mM ID 1101; Black bars: 0.5 mM ID 1101.

Detailed Description of the Invention

The invention provides methods and pharmaceutical kits or compositions for use in treating diabetes and related diseases or conditions, such as metabolic syndrome. The invention is based on the administration of hydroxylated amino acids, such as 4-hydroxyisoleucine, to patients with one or more other antidiabetic agents, in order to obtain an improved (e.g., synergistic or additive) effect. As is discussed further below, examples of agents that can be administered with hydroxylated amino acids, such as 4-hydroxyisoleucine, according to the invention, include insulin, biguanides, sulfonylureas, glinides, glitazones, glucagon like peptide-1 (GLP-1) and agonists thereof, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, and other agents mentioned herein. The methods and compositions of the invention are described in further detail, as follows.

Hydroxylated Amino Acids

Central to the invention is the administration of one or more hydroxylated amino acids (e.g., mono-hydroxylated amino acids, poly-hydroxylated amino acids, or lactonic forms of such hydroxylated amino acids), in combination with one or more other antidiabetic agents, to patients. A specific example of a hydroxylated amino acid that can be used in the invention is 4-hydroxyisoleucine (e.g., the 2S,3R,4S isomer), which has been shown both to stimulate insulin secretion in a glucose dependent manner, and to decrease insulin resistance (see, e.g., U.S. Patent No. 5,470,879; WO 01/15689; Broca et al., Am. J. Physiol. 277:E617-E623, 1999; the teachings of each of which are incorporated herein by reference).

4-hydroxyisoleucine for use in the invention can be obtained, for example, by chemical synthetic methods. However, this compound is naturally present in high quantities in the seeds of the legume fenugreek (*Trigonella foenum-graecum L.*), from which it can be purified using methods such as those described in U.S. Patent No. 5,470,879, WO 97/32577, WO 01/72688, and Wang et al., Eur. J. Org. Chem. 834-839, 2002, the teachings

**Objective:**

The objective of this study was to determine the effect of Rosiglitazone and ID 1101, alone and in combination, on glucose tolerance in mice rendered hyperglycemic by consuming a high fat diet.

**Materials and Methods:**

C57BL6 mice were received at 7-8 weeks of age and fed a high fat diet (45% of calories from fat) for 8 weeks. Blood glucose was checked and animals with readings between 200 and 220 mg/dL were randomized into control and treatment groups. A group of C57BL6 mice receiving a normal diet was included as a control.
Treatment groups included those receiving twice daily treatment by oral gavage with Rosiglitazone (1.5 or 5 mg/kg), ID 1101 (50 or 100 mg/kg), or a combination of Rosiglitazone and ID 1101 (1.5 and 50 mg/kg, respectively).

A baseline oral glucose tolerance test (OGTT) was administered prior to commencement of treatment. The test was repeated on days 7, 14, and 21, to determine whether the treatments influenced glucose tolerance.

**Results:**

As expected, the baseline OGTT showed that the animals receiving the high fat diet exhibited less tolerance to the glucose challenge than did the normal diet control (NDC) animals ($p<0.05$) (Figures 2A, 2B, 2C and 2D). On day 7, the animals underwent an OGTT and the results were compared between groups. The animals treated with the combination of ID 1101 (50 mg/kg) and Rosiglitazone (1.5 mg/kg) were significantly more tolerant to the glucose challenge relative to the high fat diet control animals (DIO) ($p<0.05$). Similarly, animals treated with Rosiglitazone at 5 mg/kg also were more glucose tolerant that the high fat diet control animals ($p<0.05$). While there was a trend indicating the drug combination may be more efficacious, the outcome was not statistically significant.

Results of the Day 14 OGTT showed a similar but non-significant trend. However, by Day 21, only the mice receiving Rosiglitazone (1.5 or 5 mg/kg) showed significantly improved glucose tolerance relative to the high fat diet control animals ($p<0.05$)

What is claimed is:

1. Use of 4-hydroxyisoleucine and one or more antidiabetic agents in the manufacture of a medicament for treating diabetes, wherein the additional antidiabetic agent(s) is selected from the following types of antidiabetic agents: biguanides, sulfonylurea drugs, glinides, insulin-sensitizing agents, glucagon-like peptide 1 receptor agonists, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, imidazolines, glycogen phosphorylase inhibitors, oxadiazolidinediones, dipeptidyl peptidase-IV inhibitors, protein tyrosine phosphatase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 inhibitors, antihyperlipidemic agents, antilipidemic agents, peroxisome proliferator-activated receptor agonists, retinoid X receptor agonists, and antihypertensive agents.

2. The use of claim 1, wherein the 4-hydroxyisoleucine is the 2S,3R,4S isomer of 4-hydroxyisoleucine.

3. The use of claim 1 or 2, further comprising use of insulin in the preparation of said medicament.

4. The use of any one of claims 1 to 3, wherein the additional antidiabetic agent is a biguanide.

5. The use of claim 4, wherein the biguanide is metformin.

6. The use of any one of claims 1 to 3, wherein the additional antidiabetic agent is a sulfonylurea drug.

7. The use of any one of claims 1 to 3, wherein the additional antidiabetic agent is a glinide.

8. The use of any one of claims 1 to 3, wherein the additional antidiabetic agent is an insulin-sensitizing agent.

9. The use of claim 8, wherein the insulin-sensitizing agent is a thiazolidinedione.

10. The use of claim 9, wherein the thiazolidinedione is rosiglitazone maleate or pioglitazone.

11. The use of any one of claims 1 to 3, wherein the additional antidiabetic agent is a glucagon-like peptide 1 receptor agonist.

12. The use of claim 11, wherein the glucagon-like peptide 1 receptor agonist is Exenatide®.

13. The use of any one of claims 1 to 3, wherein the diabetes is type 2 diabetes.

14. A pharmaceutical kit comprising 4-hydroxyisoleucine and one or more antidiabetic agents selected from the following types of antidiabetic agents: biguanides, sulfonylurea drugs, glinides, insulin-sensitizing agents, glucagon-like peptide 1 receptor agonists, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, imidazolines, glycogen phosphorylase inhibitors, oxadiazolidinediones, dipeptidyl peptidase-IV inhibitors, protein tyrosine phosphatase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 inhibitors, antihyperlipidemic agents, antilipidemic agents, peroxisome proliferator-activated receptor agonists, retinoid X receptor agonists, and antihypertensive agents.

15. The pharmaceutical kit of claim 14, wherein the 4-hydroxyisoleucine is the 2S,3R,4S isomer of 4-hydroxyisoleucine.

16. The pharmaceutical kit of claim 14 or 15, wherein the kit further comprises insulin.

17. The pharmaceutical kit of any one of claims 14 to 16, wherein the additional antidiabetic agent is a biguanide.

18. The pharmaceutical kit of claim 17, wherein the biguanide is metformin.

19. The pharmaceutical kit of any one of claims 14 to 16, wherein the additional antidiabetic agent is a sulfonylurea drug.

20. The pharmaceutical kit of any one of claims 14 to 16, wherein the additional antidiabetic agent is a glinide.

21. The pharmaceutical kit of any one of claims 14 to 16, wherein the additional antidiabetic agent is an insulin-sensitizing agent.

22. The pharmaceutical kit of claim 21, wherein the additional antidiabetic agent is a thiazolidinedione.

23. The pharmaceutical kit of claim 22, wherein the thiazolidinedione is rosiglitazone maleate or pioglitazone.

24. The pharmaceutical kit of any one of claims 14 to 16, wherein the additional antidiabetic agent is a glucagon-like peptide 1 receptor agonist.

25. The pharmaceutical kit of claim 24, wherein the glucagon-like peptide 1 receptor agonist is Exenatide®.

26. The pharmaceutical kit of any one of claims 14 to 16, wherein the hydroxylated amino acid and the additional antidiabetic agent are formulated into a single composition.

27. The pharmaceutical kit of claim 26, wherein the single composition is a tablet or a capsule.

28. A pharmaceutical composition comprising 4-hydroxyisoleucine, one or more antidiabetic agents and a pharmaceutically acceptable excipient, wherein said additional antidiabetic agent(s) is selected from the following types of antidiabetic agents:

biguanides, sulfonylurea drugs, glinides, insulin-sensitizing agents, glucagon-like peptide 1 receptor agonists, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, imidazolines, glycogen phosphorylase inhibitors, oxadiazolidinediones, dipeptidyl peptidase-IV inhibitors, protein tyrosine phosphatase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 inhibitors, antihyperlipidemic agents, antilipidemic agents, peroxisome proliferator-activated receptor agonists, retinoid X receptor agonists, and antihypertensive agents.

29. Use of a pharmaceutical kit according to any one of claims 14 to 27, or of a pharmaceutical composition according to claim 28, for treating diabetes in a patient.

30. A method of treating diabetes in a patient, the method comprising administering to the patient 4-hydroxyisoleucine and one or more additional antidiabetic agents selected from the following types of antidiabetic agents: biguanides, sulfonylurea drugs, glinides, insulin-sensitizing agents, glucagon-like peptide 1 receptor agonists, agents that slow carbohydrate absorption, glucagon antagonists, glucokinase activators, imidazolines, glycogen phosphorylase inhibitors, oxadiazolidinediones, dipeptidyl peptidase-IV inhibitors, protein tyrosine phosphatase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis or glycogenolysis, glucose uptake modulators, glycogen synthase kinase-3 inhibitors, antihyperlipidemic agents, antilipidemic agents, peroxisome proliferator-activated receptor agonists, retinoid X receptor agonists, and antihypertensive agents.

31. The method of claim 30, wherein the 4-hydroxyisoleucine is the 2S,3R,4S isomer of 4-hydroxyisoleucine.

32. The method of claim 30, further comprising administering insulin to the patient.

33. The method of claim 30, wherein the additional antidiabetic agent is a biguanide.

34. The method of claim 33, wherein the biguanide is metformin.

35. The method of claim 30, wherein the additional antidiabetic agent is a sulfonylurea drug.

36. The method of claim 30, wherein the additional antidiabetic agent is a glinide.

37. The method of claim 30, wherein the additional antidiabetic agent is an insulin-sensitizing agent.

38. The method of claim 37, wherein the insulin-sensitizing agent is a thiazolidinedione.

39. The method of claim 38, wherein the thiazolidinedione is rosiglitazone maleate or pioglitazone.

40. The method of claim 30, wherein the additional antidiabetic agent is a glucagon-like peptide 1 receptor agonist.

41. The method of claim 40, wherein the glucagon-like peptide 1 receptor agonist is Exenatide®.

42. The method of claim 30, wherein the diabetes is type 2 diabetes.

43. The method of claim 30, wherein the hydroxylated amino acid is administered to the patient at or about the same time as the additional antidiabetic agent.

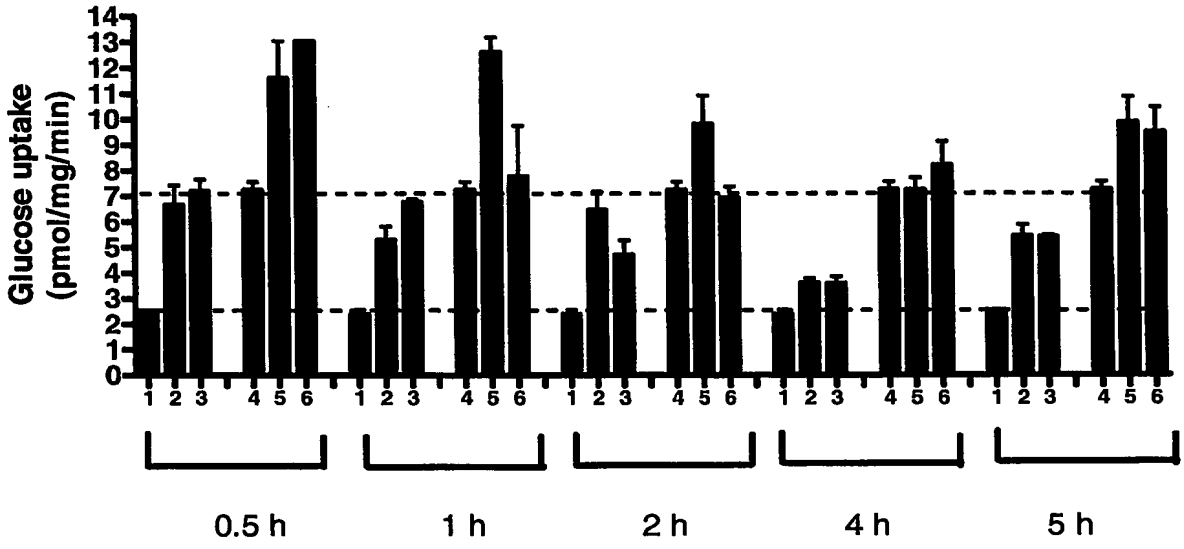
Glucose uptake
(pmol/mg/min)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1 2 3 4 5 6
0.5 h
1 h
2 h
4 h
5 h

Figure 1

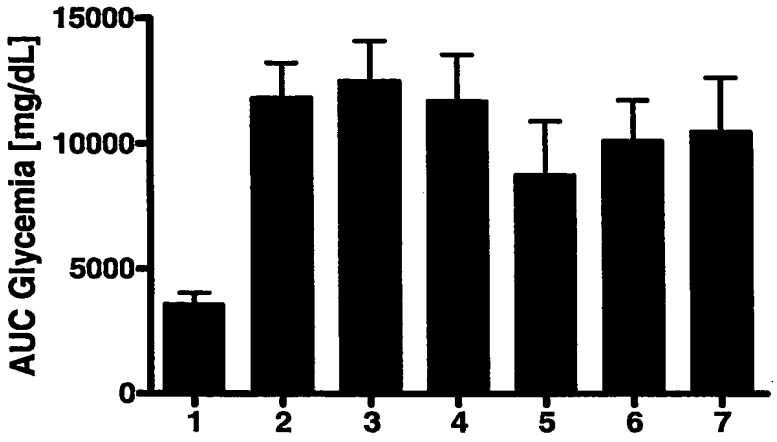


Figure 2A

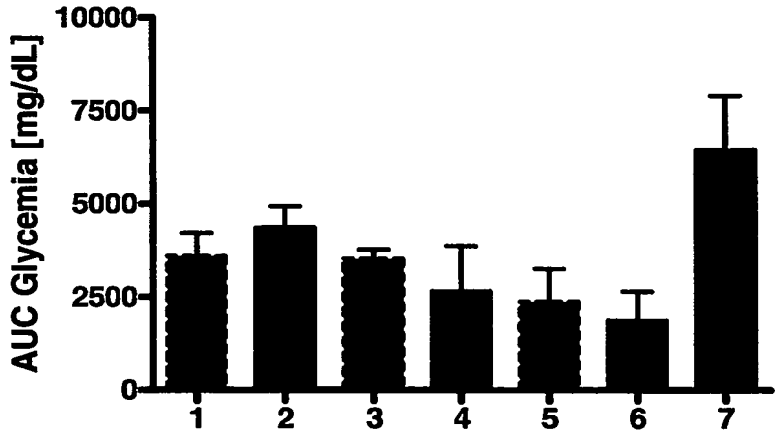


Figure 2B

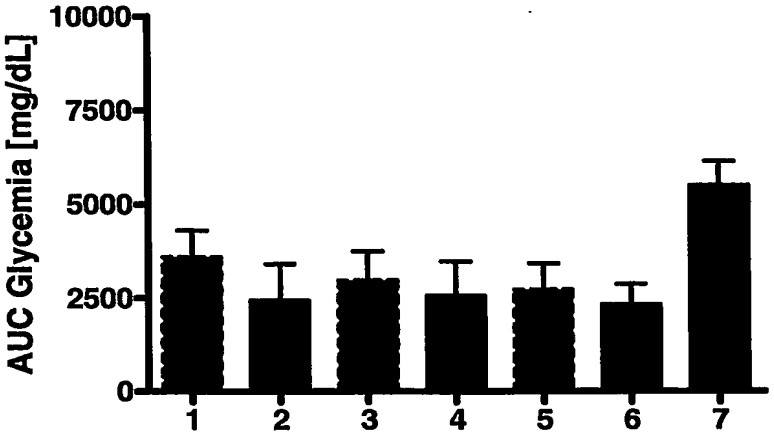


Figure 2C

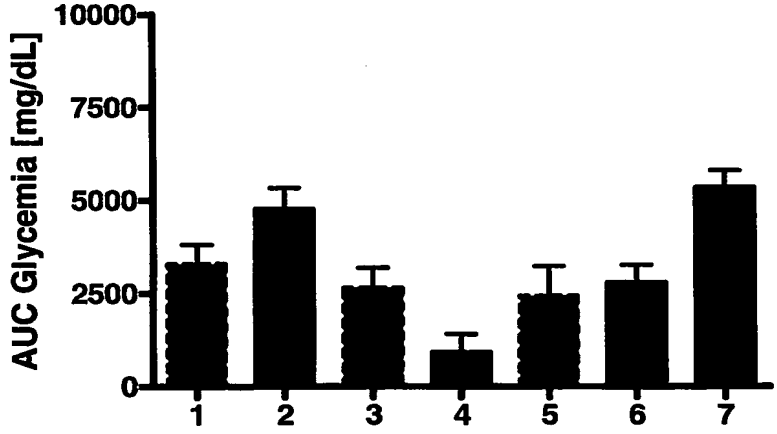


Figure 2D

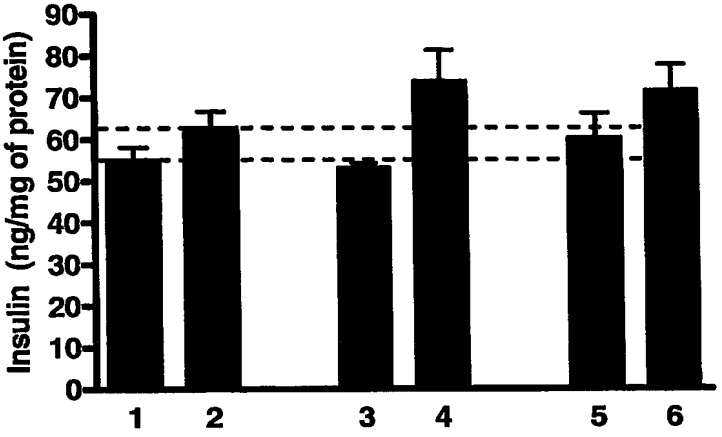


Figure 3

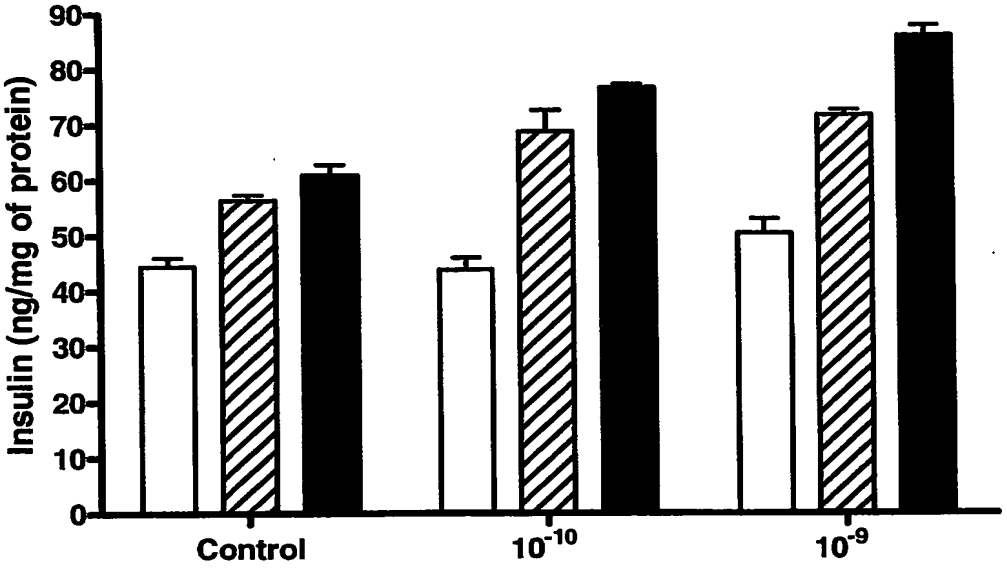


Figure 4